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External Validation of The USALFSG Acute Liver Failure Outcome Prediction Criteria

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INTRODUCTION

The new United States Acute Liver Failure Study Group (USALFSG) model to predict 21-day survival without liver transplantation (LT) in patients with acute liver failure (ALF) is based upon encephalopathy (HE) grade, vasopressor requirement, etiology Bilirubin and INR (figure 1). Derivation studies suggest good discrimination and high specificity in predicting transplant free survival. A threshold of <20% predicted survival has been suggested to identify LT candidates. The model has not been externally validated: in a large cohort of ALF patients we assessed its diagnostic performance and practical utility.

Figure 1. ALFSG Survival Prediction Model.

Log Odds of Spontaneous survival = 2.67 - 0.95 (HE*) + 1.56 (Etiology*) - 1.25(Vasopressor Use) – 0.70 (ln bilirubin) - 1.35 (ln INR).

Where:

*HE:

0= Grade 1 or 2

1= Grade 3 or 4

*Etiology:

1= Favourable (Paracetamol/Pregnancy/Ischemia/HAV)

0= Unfavourable (all others)

Source: Clin Gastroenterol Hepatol 2016 Aug;14(8):1199-1206.

PATIENTS AND METHODS

- Study cohort drawn from 2 UK sites between 1998-2016
- 1223 subjects.
 - 869 Favourable etiologies
 - 354 Unfavorable etiologies
- 236 (19%) died without transplantation
- 792 (65%) survived with medical management
- 195 (16%) underwent transplantation
- Hospital survival as primary outcome
- Diagnostic test performance assessed using Area Under Receiver Operating Characteristics (AUROC) techniques and standard approaches with and without classification of transplanted patients as 'non-survivors'.

Table 1. Admission Clinical Features of Study Cohort.

Variable	Died	Transplanted	Survived	All
Favourable (n)	160	75	634	869
HE Grade >2 (n)	77 (48%)	31 (41%)	97 (15%)	205 (24%)
INR	6.4 (3.9-9.7)	7.9 (6.4-10.8)	4.2 (2.7-6.1)	4.6 (3.0-7.2)
Bilirubin (mg/dl)	4.3 (3.1-6.8)	4.2 (3.0-5.7)	4.5 (3.0-5.7)	4.4 (3.0-6.4)
Vasopressors(n)	141 (88%)	56 (75%)	145 (23%)	342 (39%)
Unfavourable (n)	76	120	158	354
HE Grade >2 (n)	27 (36%)	33 (28%)	21 (13%)	81 (23%)
INR	3.8 (2.3-7.8)	3.6 (2.7-5.3)	2.2 (1.5-3.8)	3.0 (2.0-4.9)
Bilirubin (mg/dl)	15.8 (7.4-24.2)	22.7 (12.3-26.7)	9.5 (3.8-22.1)	15.9 (6.4-24.8)
Vasopressors (n)	46 (60%)	37 (31%)	22 (14%)	105 (30%)

RESULTS

Table 2. Predicted Survival in Cohort by Etiology and Outcome.

	Died	Transplanted	Survived	All
Favourable (n)	160	75	634	869
Predicted Survival	28% (17-49)	28% (18-41)	73% (54-84)	64% (34-81)
Un favourable (n)	76	120	158	354
Predicted Survival	11 (4-22)	17% (7-29)	46 (26-57)	25% ((9-48%)
All	236	195	792	1223
Predicted Survival	22% (12-41)	22% (10-34)	68% (45-82)	52% (24-76)

Figure 2. Area Under Receiver Operating Characteristic Curves for Predicted survival.

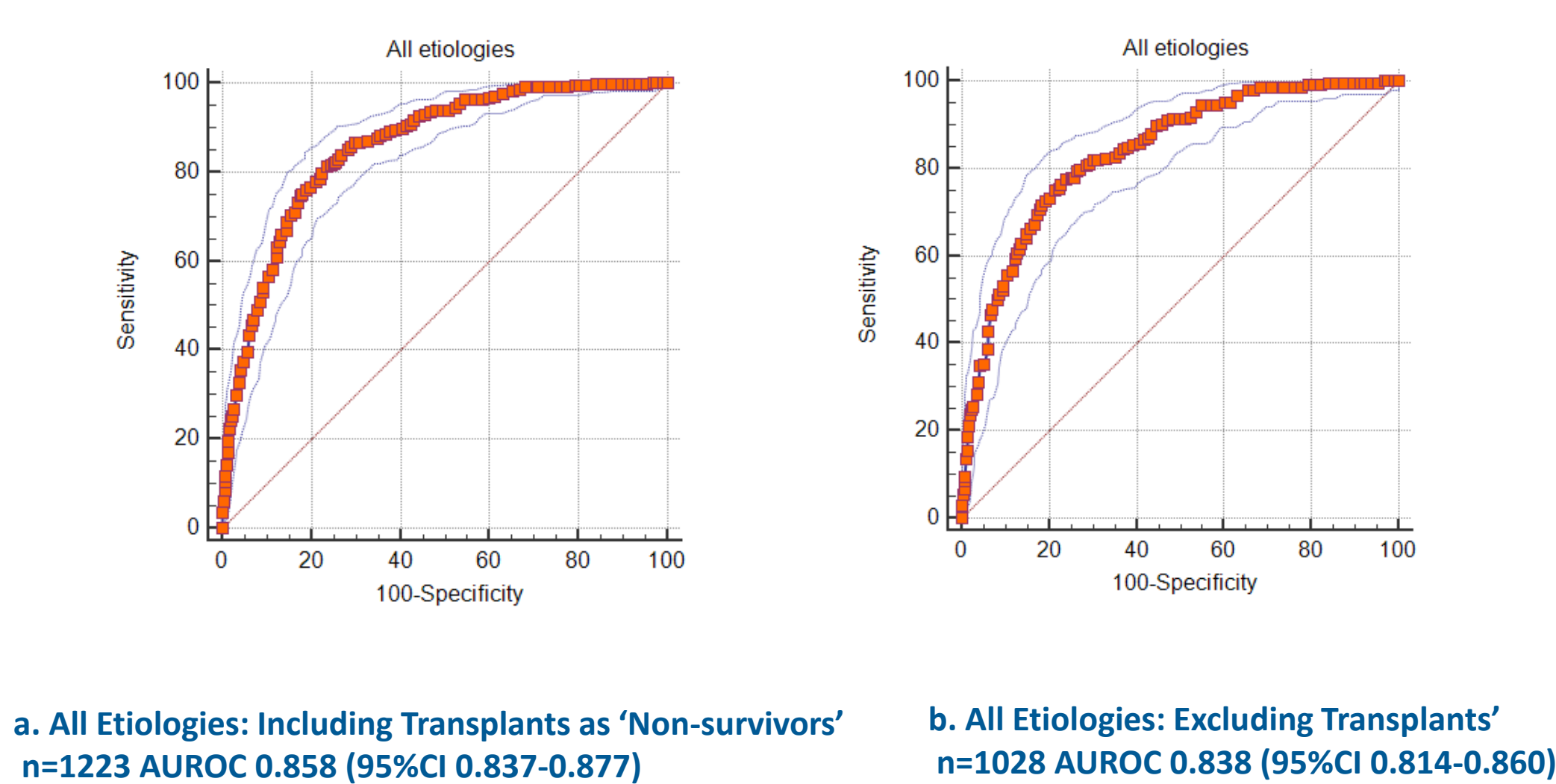
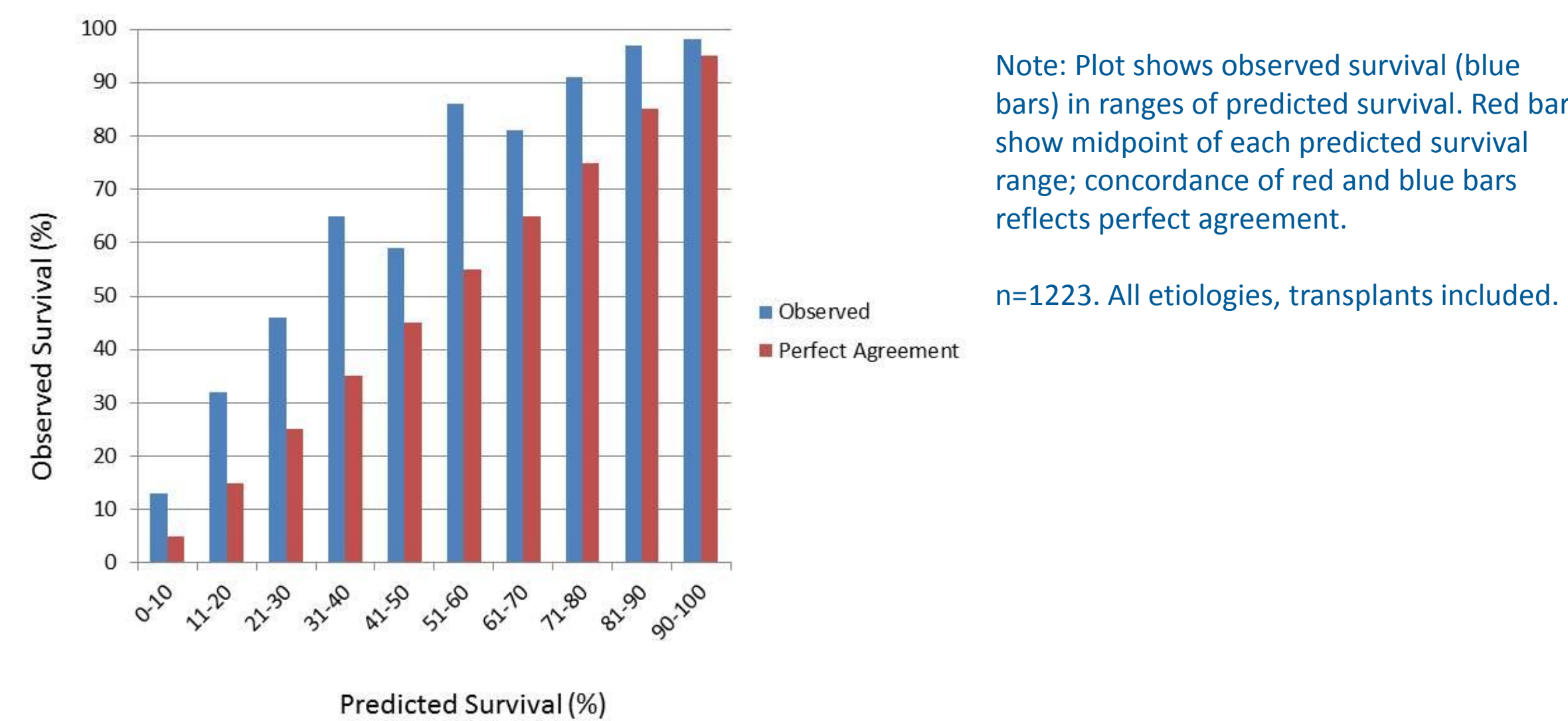


Table 3. AUROC in Cohort by Etiology and Outcome.

	Including Transplants			Excluding Transplants		
Etiology	n	AUROC	95% CI	n	AUROC	95% CI
Favourable	869	0.852	0.825-0.880	794	0.838	0.804-0.872
Un favourable	354	0.811	0.766-0.856	234	0.829	0.773-0.886
All	1223	0.858	0.837-0.879	1028	0.838	0.810-0.866
HE ≤2 Only	937	0.863	0.837-0.888	806	0.824	0.785-0.863
HE >2 Only	286	0.759	0.703-0.816	222	0.726	0.660-0.792

Figure 3. Calibration of predictive model.



Note: Plot shows observed survival (blue bars) in ranges of predicted survival. Red bars show midpoint of each predicted survival range; concordance of red and blue bars reflects perfect agreement.

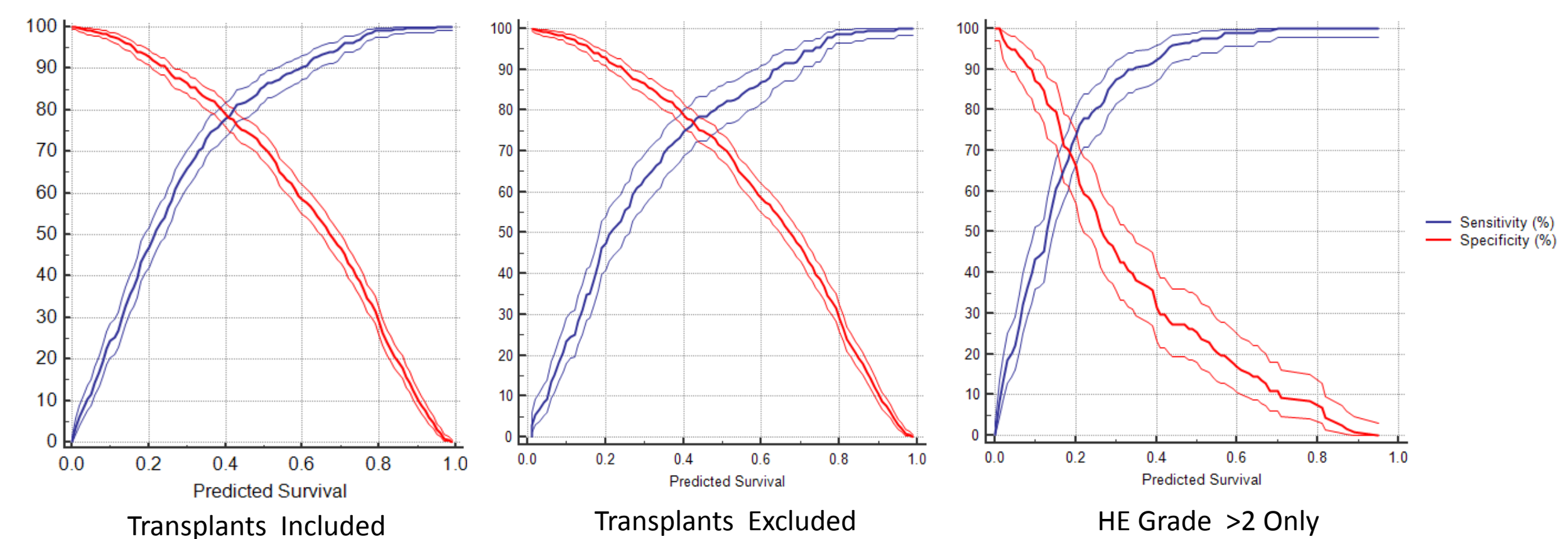
n=1223. All etiologies, transplants included.

Table 4. Diagnostic test performance of predicted survival thresholds.

Predicted Survival	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI
≤ 10%	24.36	20.4 - 28.7	97.85	96.6 - 98.7	11.35	6.9 - 18.7	0.77	0.7 - 0.8
≤ 20%	46.87	42.1 - 51.7	92.93	90.9 - 94.6	6.63	5.1 - 8.7	0.57	0.5 - 0.6
≤ 30%	65.89	61.2 - 70.4	86.62	84.0 - 88.9	4.92	4.1 - 6.0	0.39	0.3 - 0.5
≤ 40%	77.96	73.7 - 81.8	78.79	75.8 - 81.6	3.68	3.2 - 4.2	0.28	0.2 - 0.3
≤ 50%	85.61	81.9 - 88.8	70.96	67.7 - 74.1	2.95	2.6 - 3.3	0.2	0.2 - 0.3
≤ 60%	90.49	87.3 - 93.1	58.59	55.1 - 62.0	2.18	2.0 - 2.4	0.16	0.1 - 0.2
≤ 70%	95.36	92.9 - 97.1	46.59	43.1 - 50.1	1.79	1.7 - 1.9	0.1	0.06 - 0.2
≤ 80%	99.07	97.6 - 99.7	23.86	20.9 - 27.0	1.3	1.3 - 1.4	0.039	0.01 - 0.1

Note: n=1223. All etiologies, transplants included.
95%CI; 95% Confidence Interval, +LR; positive likelihood ratio, -LR; negative likelihood ratio.

Figure 4. Diagnostic test performance of predictive model.



Note: Plot shows Sensitivity (blue line) and specificity (red line) for thresholds of predicted survival. Fainter lines show 95% confidence intervals.

RESULTS

Table 5. Illustrative 2x2 Contingency Tables for 20% Predicted Survival Threshold.

a. All cases n=1223. Transplants included as non-survivors.

Predicted Survival	Non-Survivor	Survivor	
≤ 20%	202	56	258
> 20%	229	736	965
	431	792	1223
Specificity	Sensitivity		Accuracy
92.9% (90.9-94.6)	46.9% (42-51.7)		76.7 (74.6-78.5)

b. HE grade >2 cases only n=286. Transplants included as non-survivors.

Predicted Survival	Non-Survivor	Survivor	
≤ 20%	124	40	164
> 20%	44	78	122
	168	118	286
Specificity	Sensitivity		Accuracy
66.1% (59.1-72.5)	73.8% (68.9-78.3)		70.6% (64.8-75.9)

CONCLUSIONS

External assessment of the USALFSG model to predict medical survival of ALF patients confirms:

- Simplicity of use with readily available variables.
- Good discrimination as assessed by AUROC.
- Reasonable calibration.
- Predicted survival threshold of <20% for identifying non-survivors had high specificity but low sensitivity, failing to identify half of non-survivors.
- Model is unlikely to be sole tool to select LT candidates.

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